GREMLIN-1 ANTAGONIST FOR THE PREVENTION AND TREATMENT OF CANCER

FIELD OF THE INVENTION

[0001] The present invention relates to an anti-GREM1 antagonist for use in a method of treatment of cancer. The cancer is typically a solid cancer having a stroma, typically having stromal GREM1 overexpression. The cancer may have epithelial GREM1 overexpression. The present invention further relates to combination therapy with a GREM1 antagonist and an additional anti-cancer (such as chemotherapeutic) agent, and related compositions. The present invention also relates to detection, prognosis and selections of treatment for cancer based on stromal GREM1 overexpression.

BACKGROUND TO THE INVENTION

[0002] Gremlin-1 (also known as Drm and CKTSF1B1 and GREM1) is a 184 amino acid glycoprotein which forms part of the DAN family of cystine-knot secreted proteins (along with Cerberus and Dan amongst others). GREM1 binds and inhibits the ability of BMP-2, 4, and 7 to signal along with a documented pro-angiogenic role possibly through agonism of VEGFR2. The main role of GREM1 is during development, in which it is vital during kidney formation and during limb bud formation. These vital roles make GREM1 homozygous knock-outs embryonic lethal in mice.

[0003] In adulthood, increased levels of GREM1 have been associated with idiopathic pulmonary fibrosis and pulmonary arterial hypertension in which BMP2, 4 and 7 signalling is reduced with an associated rise in TGFP levels. In both diabetic and chronic allograft nephropathy, GREM1 expression has been correlated with fibrosis score.

[0004] Increased levels of GREM1 have also been associated inter alia with scleroderma, diabetic nephropathy, glioma, head and neck cancer, prostate cancer and colorectal cancer (Sneddon et al; Guan et al). GREM1 has been shown to activate cancer cell invasion and proliferation in vitro and is thought to play a role in uterine, cervix, lung, ovary, kidney, breast, colon, pancreatic and sarcoma carcinomas.

[0005] There is a need to identify effective therapies for use in treatment and prevention of cancer.

SUMMARY OF THE INVENTION

[0006] The inventors have surprisingly shown that GREM1 antagonists are effective therapeutic and preventative agents against neoplasia with stromal and/or epithelial GREM1 overexpression, including colorectal cancer and multiple myeloma. It is envisaged by the inventors based on these results that GREM1 antagonists will be of general utility in treatment and prevention of cancer, including other cancers having stromal GREM1 overexpression. The in vivo results provided herein illustrate long-term prevention of induction of neoplasia in various mouse tumour models by administration of a GREM1 antagonist, and significant therapeutic impact on existing tumours by administration of a GREM1 antagonist. The inventors' findings thus provide for a new approach to prevention and treatment of cancer, including in cancers resistant to standard chemotherapeutic agents.

[0007] Thus, in a first aspect of the present invention there is provided an anti-GREM1 antagonist for use in a method for the treatment or prevention of a cancer.

[0008] In a further aspect of the invention, there is provided an anti-cancer agent for use in a method for the treatment of a cancer wherein the method comprises separate, sequential or simultaneous administration of an anti-GREM1 antagonist.

[0009] In another aspect of the invention, there is provided a method of treating a cancer comprising administering a therapeutically effective amount of an anti-GREM1 antagonist to a subject in need thereof. In yet another aspect of the invention, there is provided a composition or kit comprising an anti-GREM1 antagonist and an additional anti-cancer agent.

[0010] In a further aspect of the invention, there is provided a method for detecting cancer in a patient, the method comprising measuring stromal expression of GREM1 in the patient, wherein stromal overexpression of GREM1 indicates that the patient comprises a cancer.

[0011] In yet a further aspect of the invention, there is provided a method for prognosing a cancer in a patient, the method comprising determining whether or not the cancer comprises stromal overexpression of GREM1, wherein stromal overexpression of GREM1 in the cancer indicates that the patient has a worse prognosis than in the situation of normal stromal expression of GREM1.

[0012] In another aspect of the invention, there is provided a method for determining whether or not a patient having or suspected of having or being at risk of developing cancer is likely to respond to treatment with a chemotherapeutic agent, which method comprises measuring stromal expression of GREM1 in the patient, and thereby predicting whether or not the patient is likely to respond to treatment with the chemotherapeutic agent. In yet another aspect of the invention, there if provided a method for determining whether or not a patient having or suspected of having or being at risk of developing cancer is likely to respond to treatment with a GREM1 antagonist, the method comprising measuring stromal expression of GREM1 in the patient, and thereby predicting whether or not the patient is likely to respond to treatment with the GREM1 antagonist.

BRIEF DESCRIPTION OF THE FIGURES

[0013] FIG. **1**. Percentage restoration of signal for the immunisation derived antibodies in the HEK-ID1 reporter gene assay.

[0014] FIG. **2**. Percentage restoration of signal for library derived antibodies in the HEK-ID1 reporter gene assay.

[0015] FIG. **3**. Results for the HEK-ID1 reporter gene assay with titrations of human Gremlin (FIG. **3**A) and mouse Gremlin (FIG. **3**B) and the effect of antibody 7326 (shown as antibody PB376) in restoring signalling of BMP.

[0016] FIG. **4**. A structural model of the Gremlin-Fab complex, with the possible BMP binding regions and the Fab epitope highlighted.

[0017] FIG. **5**. Organoid culture from mouse intestinal crypts at day 0 and day 7 following seeding. Media contains recombinant protein supplementation and/or test anti-Grem1 antibody. E=Epidermal growth factor, G=Grem1, R=Rspo1.

[0018] FIG. **6**. Western blot on proteins extracted from Vil1-Grem1 mouse epithelium. 6 weeks of antibody administration at 30 mg/kg is able to restore epithelial pSMAD1,5 signalling.